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Fibroblast Growth Factors in Schizophrenia

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A large association study by O'Donovan et al recently suggested that genetic variation in *fibroblast growth factor receptor (FGFR) 2* increases the risk for developing schizophrenia. Fibroblast growth factors (FGFs) are part of the family of glial growth factors; they control the growth and patterning of specific brain structures and regulate the maintenance and repair of neuronal tissues. In addition, a direct interaction was recently found between FGFRs and adenosine A_{2A} receptors, leading to corticostriatal plasticity and antagonizing the signaling pathway of dopamine D_2 receptors. These findings make *FGFs* plausible candidate genes for schizophrenia. Here, we review the role of FGFs in schizophrenia and combine evidence from studies on variations in *FGF* genes, RNA expression, protein levels, and FGF administration, as well as the effects of medication and environmental risk factors for schizophrenia. These data suggest that changes in the FGF system contribute to schizophrenia and possibly to a wider range of psychiatric disorders. The role of FGFs in schizophrenia and related disorders needs to be studied in more detail.

Key words: glia/neurodevelopment/neurotrophic/genetics/dopamine/psychosis

Introduction

One of the current leading hypotheses on the pathogenesis of schizophrenia concerns impairments in connectivity between different brain regions.[1] Theoretically, the connectivity of neurons can be impaired by abnormalities in axons, myelin or synaptic transmission, or a combination of these. Evidence is now converging from molecular, gene expression and neuroimaging studies to support the involvement of myelin and white matter abnormalities in schizophrenia.[2,3] For synapses, it has been hypothesized that synaptic destabilization, leading to reduced synaptic strength, is caused by deficiencies in glial growth factors.[4] The hypothesis is supported by findings of glial cell loss, decreased expression of glia-related genes and increased S100B (a marker of glia cell integrity) in schizophrenia patients.[4] Examples of glial growth factors include neuregulin, neurotrophins, insulin-like growth factor (IGF) 1, epidermal growth factor (EGF), and fibroblast growth factor (FGF). Some of these factors, such as FGF, EGF, and IGF, were first recognized as having effects on nonneural tissues but were later found to exert neurotrophic effects as well.[5] Other factors, including brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, and nerve growth factor, were primarily found to be involved in neuronal regulation and were therefore called neurotrophins.[5] Several of these genes, including *neuregulin 1* and *BDNF* have been identified as candidate genes for schizophrenia in association studies.[6,7]

Here, we will review the possible relationship between FGFs and schizophrenia and summarize findings from functional, genetic, and expression studies and from studies on environmental risk factors of schizophrenia, psychoactive medication, and the administration of FGFs. We have covered both human and animal studies and will discuss their implications for our understanding of the pathophysiology of schizophrenia and for future research on this disease.

Fibroblast Growth Factors

FGFs are signaling proteins that influence the development and repair of virtually all mammalian tissues.[8] They are expressed during embryonic development, postnatally, and in adulthood. During development, FGFs control the growth and patterning of several brain structures, while later in life, they continue to regulate neurogenesis, axonal growth, neuroprotection, learning, memory, and the maintenance and repair of neuronal tissues.[8] In addition, growth factors such as FGF2 govern oligodendrocyte numbers, differentiation, phenotype divergence, and myelinogenesis.[9,10]

In humans, 22 FGFs and 5 fibroblast growth factor receptors (FGFRs) have been identified.[11] All these

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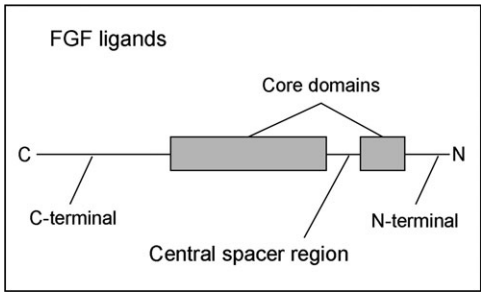

Fig. 1. The Structure of FGF Ligands. All FGFs consist of 2 highly conserved core domains, separated by a central spacer region of variable length; the C- and N- terminal regions also differ in length.

FGFs consist of 2 highly conserved core domains, separated by a central spacer region of variable length, with C- and N- terminal regions that also differ in length (figure 1). [11] FGFRs consist of 3 extracellular immuoglobulin-like domains, 1 transmembrane domain, and 2 intracellular tyrosine kinase domains. Only the fifth FGFR has no intracellular tyrosine kinase domain and little resemblance (32%) in the extracellular domain, leading to a controversy about the grouping of this receptor in the FGFR family.[12]

How do FGFs work? They are secreted into the extracellular space upon cell damage.[8] After ligand binding, a complex of 2 FGF molecules is formed, bound to a receptor and linked by heparan sulphate proteoglycan such as heparin.[8] Formation of this complex triggers receptor activation by phosphorylation, leading to recruitment and phosphorylation of intracellular signaling molecules. The principal difference between the first 4 FGFRs is the strength of tyrosine kinase activity they provoke, rather than any differences in their target proteins.[13]

Of all FGFs, FGF1 and FGF2 have been investigated most thoroughly. Both are widely distributed throughout the central nervous system. FGF1 is expressed predominantly in neurons in the cerebellum, locus coeruleus, hippocampus, and neocortex,[8] while FGF2 is expressed in specific populations of neurons, such as in the CA2 field of the hippocampus, the substantia nigra, and the striatum.[14] FGF2 is also expressed in glial cells and has been detected in the substantia nigra, striatum, medulla oblongata, pons, colliculi, thalamus, olfactory bulb, and the cerebral cortex.[8] Both FGF1 and FGF2 have neuroprotective properties, for instance, FGF2 decreases ischemic injury, glutamate-induced neuronal cell death, and death of midbrain dopamine neurons after various toxic insults (eg, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] and 6-hydroxydopamine).[8,15,16] It is thought that FGF1 might also play a role in learning and memory by generating long-term potentiations.[8] Specific functions are, however, only known for a few other FGFs. For example, FGF22 plays an important role in the communication between axon and target during synapse formation and differentiation.[17] It has been identified as a target-derived presynaptic organizer. FGF8 and FGF17 are expressed at the midbrain-hindbrain boundary and are involved in patterning and development of the midbrain, isthmus, and cerebellum.[18]

Studies of FGFRs have been confined mainly to FGFR1, FGFR2, and FGFR3.[11] FGFR1 is widely distributed throughout the nervous system, while FGFR2 and FGFR3 have a more distinct anatomical and temporal distribution.[11] FGFR1 is necessary for hippocampal growth and proliferation of neural stem cells.[19] FGFR2 is expressed in the embryo, predominantly in neurons of mesencephalon and telencephalon, whereas in adulthood, expression switches to glial cells. FGFR3 is expressed in glial cells of diencephalon and myelencephalon during development, with expression patterns widening during adulthood.[11]

FGFs and Psychiatric Disorders

A role for FGFs in the etiology of psychiatric disorders in general[20] and in mood disorders in particular[11] has been suggested based on the neurodevelopmental functions of FGFs, increased expression of FGF2 and FGFR3 after treatment with selective serotonin reuptake inhibitors (SSRIs), and reduced FGF2 expression found in the postmortem brains of depressed patients.

As we will show, changes in the FGF system are not specific for mood disorders because FGF expression is also altered after antipsychotic treatment and in the postmortem brains of schizophrenia patients. Because mood disorders and schizophrenia show considerable clinical overlap,[21] one could expect them to share some pathophysiological mechanisms.

FGFs and Dopamine

One of the central hypotheses on the pathophysiology of schizophrenia is based on the antidopaminergic action of antipsychotic medication and the potential of dopamine agonists to induce schizophrenia-like symptoms.[22] Moreover, single-photon emission computed tomography and positron emission tomography scans show an increase in D_2 receptor density and affinity in patients with schizophrenia.[23,24] However, extensive study of the dopamine system has not demonstrated a basal hyperdopaminergic state in schizophrenia.[22] Recent models include a more complex dopamine dysregulation involving both hypo- and hyperdopaminergic brain regions, as well as disturbances in other neurotransmitter systems such as glutamate and γ-aminobutyric acid.[22,25] The causes of these disturbances still need to be determined, however.

The FGF system strongly interacts with the dopamine system. In neuronal cultures prepared from embryonic day 12 rat ventral mesencephalon, administering FGF2 led to increased proliferation and a delay in differentiation

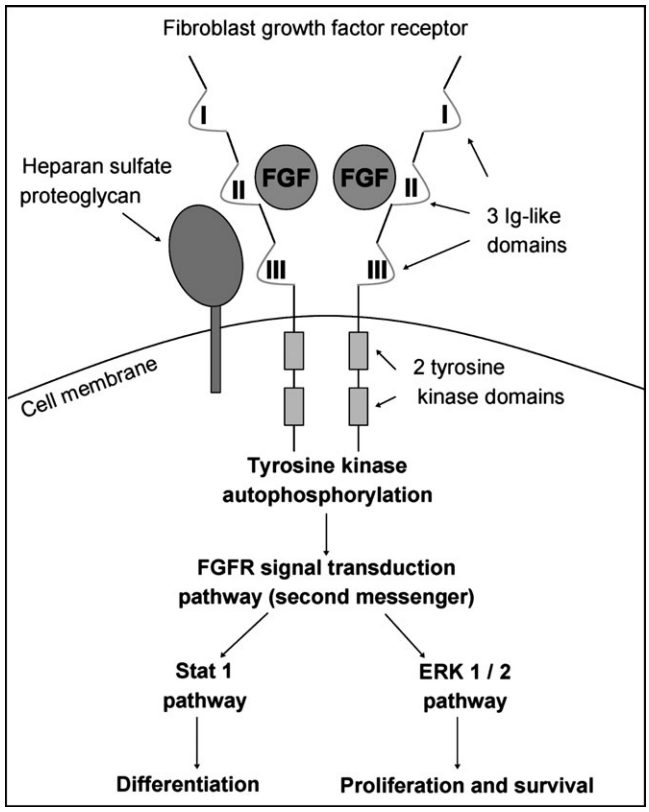

Fig. 2. Fibroblast Growth Factor (FGF) Receptor Complex and Its Schematic Signaling Pathway. After ligand binding, a complex of 2 FGF molecules, bound to a receptor and linked by heparan sulphate proteoglycan, is formed.[8] This can activate the Stat 1 or the ERK1/2 pathway.

of these dopamine precursor cells.[8] Dopamine, on the other hand, enhances release of FGF2 from astrocytes.[8,15] FGF2 subsequently binds to its receptor on dopaminergic neurons, in which 2 distinct pathways can be activated depending on the cell type.[15] The first pathway is the extracellular signal-regulated kinase (ERK) 1/2 cascade, an example of a highly conserved mitogen-activated protein kinase (MAPK) cascade, which promotes survival and proliferation, predominantly in central neurons (figure 2). The second pathway is the Stat 1 pathway, which can lead to differentiation in peripheral neurons.[15] Thus, in the nigrostriatal system, the FGF2- and FGFR3-mediated ERK1/2 pathway seems to play a key role in dopamine neuron functioning.

Signaling actions of the adenosine A_{2A} receptors are opposed by actions of dopamine D_2 receptors, which are located on the same cells. Recently, a direct physical interaction was found between FGFRs and adenosine A_{2A} receptors.[26] Concomitant activation of the FGF and adenosine A_{2A} receptors caused a robust activation of the MAPK/ERK pathway, leading to neurite extension, spine morphogenesis, and corticostriatal plasticity. The dopamine D_2 receptor agonist quinpirole was able to block the synergistic actions of FGF and adenosine A_{2A} receptors on corticostriatal plasticity. This discovery shed light on the role of FGFs, as a cotransmitter through the adenosine A_{2A} receptor, in regulating synaptic plasticity and modulating the actions of dopamine on the dopamine D_2 receptor.

Human Studies on Genetic Variation in FGF Genes

Several human genetic studies provide evidence for *FGF* genes being involved in schizophrenia. One interesting finding was the disruption of the *neuronal PAS domain protein 3 (NPAS3)* gene that was reported to cosegregate with illness in a small family with schizophrenia.[27] *NPAS3* knockout mice show an 80% reduction in FGFR1 messenger RNA (mRNA) and reduced neuronal cell proliferation in the dentate gyrus.[28] Phenotypically, these mice display impaired behavioral and neuroanatomical abnormalities similar to those observed in schizophrenia, including impaired social recognition, increased open-field locomotor activity, stereotypic darting behavior, reduced prepulse inhibition, and decreased brain levels of reelin protein. These findings make *NPAS3* and *FGFR1* interesting targets for further genetic studies in schizophrenia.

Associations between *FGF* single-nucleotide polymorphisms (SNPs) and schizophrenia have been found in studies both with and without prior hypotheses on the function of the SNPs tested. A large positional association study by O'Donovan et al[29] is an example of one in which no functional assumptions were made. After they had identified the 10q25–q26 region in linkage studies as associated with schizophrenia, they fine mapped the region by testing 3606 SNPs in 5142 schizophrenia patients and 6561 controls. Only SNP rs17101921, located 85 kilobases from the nearest gene, *FGFR2*, remained significant after several rounds of replication.

An example of a hypothesis-based association study is one conducted by our research group. Based on the theory that impaired connectivity and white matter abnormalities are part of schizophrenia, we tested 771 SNPs in 138 myelin-related genes, including 56 *FGF* SNPs. We found suggestive evidence for an association of *FGF1* and *FGFR1* genes with schizophrenia.[30] *FGFR1* SNP rs3925 was also associated with reduction in white matter volume, while there was a diagnosis-by-genotype interaction with an effect on white matter volume for *FGF1* SNP rs2070715 and an effect on gray matter volume for *FGFR1* SNP rs2288696 (M.L.C. Hoogendoorn, PhD; N.E.M. van Haren, PhD; B.J. Jungerius, PhD; S.C. Bakker, MD, PhD; R.J. Sinke, PhD; J.-P. Selten, MD, PhD; R.A. Ophoff, PhD and R.S. Kahn, MD, PhD, unpublished results, 2007). Recently, we investigated the relationship between *FGF2*, *FGFR1*, and hippocampal volume in patients with schizophrenia and healthy controls. SNP rs308379 in *FGF2* was significantly associated with hippocampal volume in patients ($P = .042$ after

stringent Bonferroni correction for testing 14 SNPs) but not in controls.[31] Lastly, *FGF1* (on chromosome 5q31) and *FGF20* (on chromosome 8p22) are located in regions that have been replicated for linkage with schizophrenia.[32,33]

Mouse Studies on Genetic Variation in FGF Genes

Two different *FGFR1* knockout mice models display "schizophrenia-like" characteristics. In the first model,[19] a *tyrosine kinase domain–deficient FGFR1 (tFGFR1)* gene construct was expressed in the mouse during embryonic brain development. This resulted in decreased thickness of the cerebral cortex in frontal and temporal areas. Interestingly, in magnetic resonance imaging studies of patients with schizophrenia, a cerebral volume reduction of about 3%, particularly in the gray matter, has repeatedly been found.[23,34] These volume reductions are most notable in frontotemporal regions, especially in the hippocampus, amygdala, the prefrontal cortex, and the superior temporal gyrus.[23,35] The reduced cortical thickness in the *tFGFR1* mouse was due to fewer pyramidal neurons and disorganization of pyramidal cell dendritic architecture.[36] These transgenic mice displayed spontaneous and persistent locomotor hyperactivity, indicating that FGF signaling is critical for inhibitory regulation of motor behavior in the dopaminergic nigrostriatal system.[36]

The second mouse model is the *FGFR1(TK-)* mouse.[24] This mouse has a *kinase-deficient FGFR1* gene, which inactivates endogenous FGFRs by heterodimerization with those receptors. This mutant gene is only expressed in tyrosine hydroxylase–positive, dopamine-producing, neurons. These mice show decreases in cell size and density in the substantia nigra and ventral tegmental area. Moreover, sensory motor processing impairments, including reduced prepulse inhibition and enhanced startle response, were seen. These impairments, which can also be observed in schizophrenia patients,[37] could be normalized with flupentixhol, which is an antipsychotic drug. Dopaminergic neurons of these transgenic mice showed reduced proliferation and differentiation, although their survival was not impaired. The authors Klejbor et al[24] concluded that their findings indicated that "either changes in *FGFR* or disruptions of pathways that utilize FGFR signaling (including cyclic adenosine monophosphate signaling pathway recently implicated in schizophrenia) may impair the development of dopamine neurons and thereby lead to a schizophrenia-like disorder".

Three other *FGF* knockout mice models display neurobiological phenotypes. In *FGF2* knockout mice, a decreased neuron number and density were found in the cerebral cortex,[38] but no significant decrease in neurons in striatum or hippocampus was seen, indicating a redundancy in the FGF system.[15,38] *FGF14*-deficient mice develop ataxia and hyperkinetic movement disorders similar to parkinsonism and dystonia[39]; these are frequently observed not only in schizophrenia patients after antipsychotic treatment but also in medication-naive patients.[40] Lastly, *FGF8* knockout mice show a disturbed development of the midbrain-hindbrain boundary.[18]

FGF mRNA Expression and Protein Levels in Schizophrenia

In a comparison of 40 schizophrenia patients and 40 controls, increased levels of FGF2 protein in serum were found in medicated patients and in nonmedicated patients who had a high subscore on negative symptoms on the brief psychiatric rating scale.[41] One study found decreased FGFR2 and slightly raised FGFR1 mRNA expression in the hippocampus of postmortem brains of schizophrenia patients (compared with control brains), together with a decreased FGFR2 expression in the cingulate cortex.[42,43]

FGF and Environmental Risk Factors for Schizophrenia

Schizophrenia is generally thought to be caused by multiple genes interacting with each other and environmental factors.[44,45] The main known environmental risk factors for schizophrenia have modest effects, with odds ratios of approximately 2. FGFs are related to the environmental risks in several different ways.

1. Smoking of cannabis is one of the most well-established environmental risks for development of schizophrenia.[46] It has been demonstrated in vitro that cannabinoid receptor CB1 *agonists* mimic the FGF2 (and *N*-cadherin) response in axonal growth at a step downstream of FGFR activation.[47] On the other hand, cannabinoid receptor CB1 *antagonists* inhibit axonal growth responses stimulated by FGF2. Because cannabis contains both CB1 partial agonist (-)-*trans*-delta9-tetrahydrocannabinol and CB1 antagonist cannabidiol,[48] it is yet unknown what the influence of smoking cannabis is on FGF2 functioning and axon outgrowth in vivo.
2. During early development, the brain is particularly sensitive to various insults from the prenatal and postnatal environment, which can lead to neuropsychiatric illness in later life. Among the possible insults in this period are viral or parasitic infections in the mother during pregnancy.[49] Offspring of mothers with serologic evidence of herpes simplex virus-2 infection were at significantly increased risk for the development of psychosis (odds ratio = 1.6), especially if they were having intercourse more than 5 times per month during pregnancy (odds ratio = 2.6).[50] The neurotropic herpes simplex virus, which is known to infect the central nervous system, uses FGFR1 to gain entry into cells.[49] Not only after infection but also after oxidative stress or famine an eukaryotic translation

initiation factor 2 alpha (EIF2alpha) kinase signaling cascade is activated, which shuts down protein synthesis.[49] Oligodendrocytes appear particularly sensitive to malfunction of this system because mutations in *eIF2b*, another member of this pathway, cause vanishing white matter disease. Oligodendrocyte cell loss or demyelination has been observed in response to infection with herpes simplex virus in vitro. The same signaling cascade is utilized by intrinsic neurotrophic factors, including several schizophrenia candidate genes, such as *BDNF* and *NRG1*.[49] Malfunction of these networks, either by variations in the candidate genes (intrinsic) or by infection with pathogens (extrinsic) may contribute to the pathological features of schizophrenia. Several genes may affect pathogen virulence, while the pathogens in turn may affect gene expression and processes relevant to the neurophysiology of schizophrenia.

3. Perinatal hypoxia, eg, due to complications during delivery, is another risk factor for schizophrenia, with odds ratios varying from 1.7 for asphyxia to 4.0 for placental abruption.[51] Because 25%–30% of births involve at least one obstetric complication, on a population level this constitutes an important risk factor.[51] In rat studies, perinatal hypoxia leads to sensitization of the dopamine system and a reduction in the expression of FGF2 in the ventral tegmental area, enhancing the responsiveness of FGF2 to stress permanently in later life.[20] After 2 weeks of chronic perinatal hypoxia, expression of FGF1 and FGF2 is increased in the immature astroglia throughout the forebrain, suggesting a functional hyperactivity of the FGF signaling system in the brain under hypoxic conditions.[52] Interestingly, one human study also found indications of disrupted neurotrophic signaling after perinatal hypoxia. This study found a significant differential response (20% decrease in patients vs 10% increase in controls) of BDNF in response to perinatal hypoxia in subjects who later developed schizophrenia compared with healthy controls.[53] This differential response could not be explained by other obstetric complications or *BDNF Val66Met* polymorphisms, but, unfortunately, other neurotrophic factors, such as FGFs, were not tested.
4. Severe stress of the mother during the first trimester, such as the death of a close relative, is associated with an increased risk for schizophrenia.[54] In rats, decreased FGF2 mRNA expression was found in the prefrontal cortex shortly after prenatal stress, while FGF2 mRNA in the entorhinal cortex and striatum was increased.[55] In adult rats who had been exposed to prenatal stress, the stress response pattern in the prefrontal cortex was reversed (stimulation instead of inhibition), whereas it was blunted in the entorhinal cortex and was desensitized in the striatum.[55] These data demonstrate that the prenatal environment can permanently alter basal expression levels as well as stress-induced changes in FGF2. The regional differences in the effect of prenatal stress on FGF2 expression might be due to differential activity of the dopaminergic system in these brain areas.[55] Stress in later life also influences FGF2: in the rat hippocampus, FGF2 mRNA was upregulated after acute and chronic stress, and this may be mediated by glucocorticoids.[56]
5. Social defeat, defined as a subordinate position or "outsider" status, is postulated to be a risk factor for schizophrenia through sensitization of the mesolimbic dopamine system.[57] In rats, the expression of FGF2 and FGFR1 mRNA, as well as BDNF, was downregulated in the hippocampus after social defeat[58]; it also decreased cell survival and proliferation in the hippocampus.[58] Because FGF2 is a potent modulator of these neuronal processes,[20] it is hypothesized that the decrease in FGF2 might be responsible for the decreased neurogenesis.

Finally, many other environmental factors are known to influence FGF expression. Repeated exposure to amphetamines or cocaine increases FGF2 expression in dopamine-producing structures in rats.[20,59] FGF2 antibodies can block the sensitization of the dopamine system after amphetamine administration,[11] which proves the necessity of FGF2 in this process. In other experiments, changes in FGF expression were found, but the actual function of FGFs has hardly been investigated. Injury, stress, seizures, learning experiences, and physical activity all increased neural firing rates in rats and thereby led to increases in FGF2 expression.[39,55] FGF2 mRNA was further upregulated in an environment that stimulated learning and memory and in the offspring of mothers who showed higher levels of pup licking and grooming (ie, increased maternal care).[58]

FGFs and Medication

Antidepressant drugs can influence FGF expression. For example, chronic administration of antidepressant drugs has been shown to upregulate FGF2 mRNA and protein in rat hippocampus and cerebral cortex.[20] In a human postmortem study, depressed subjects treated with selective serotonine reuptake inhibitors (SSRIs) showed less decrease in FGFR2 and FGFR3 mRNA expression than depressed subjects not using SSRIs.[60]

Several antipsychotic drugs have also been found to influence FGF expression. Chronic administration of clozapine, the most effective antipsychotic,[61] was shown to selectively increase FGF2 mRNA and protein expression in rat striatum but not in other brain areas such as the hippocampus or frontal or parietal cortex.[62] Other typical (haloperidol and chlorpromazine) and atypical (olanzapine and quetiapine) antipsychotic agents did not show

these effects.[62] Conversely, in a study of postmortem brains of patients with depression, bipolar disorder, or schizophrenia and of healthy controls, it was found that the expression of FGF2 mRNA in region CA1 of the hippocampus was lower in subjects receiving clozapine, compared with subjects who were not receiving clozapine.[42] It was suggested that clozapine influences the availability of FGF2 by altering the levels of heparan sulphate, a protein that binds to FGF2. An alternative explanation might be that the subjects receiving clozapine were more severely ill. Another study reported a marked elevation of FGF2 (and BDNF) mRNA levels in rat hippocampus after acute administration of quetiapine but only under conditions of reduced *N*-methyl-D-aspartic acid (NMDA) receptor activity.[63] Deficient NMDA signaling, in turn, is regarded as a key process in schizophrenia.[64] In addition, FGF2 expression in rat prefrontal cortex and hippocampus was increased after combined, but not separate, administration of fluoxetine and olanzapine.[65] Finally, acute or chronic administration of E-5842, a preferential sigma-1 receptor ligand and putative antipsychotic drug, resulted in upregulation of FGF2 mRNA in the prefrontal cortex, striatum, hypothalamus, and hippocampus in a dose-dependent manner.[66]

In conclusion, although no uniform response has been reported, several antipsychotic drugs seem to be able to upregulate FGF2 expression. However, not only dopamine antagonists but also the dopamine agonist quinpirole is capable of upregulating FGF2 mRNA in the striatum, prefrontal cortex, and hippocampus.[67] Quite how dopamine antagonists and agonists can both increase FGF2 is not yet clear, although there may be differences in the mechanisms controlling FGF2 production and subcellular localization.

Because atypical antipsychotic use is associated with an increased incidence of diabetes mellitus type 2,[68] it is interesting to note that disturbed FGFR1 and FGFR2 expression can cause diabetes type 2 in mice.[69] The influence of antipsychotic medication on FGFR1 and FGFR2 expression has not been investigated. One final interesting observation is that the benzodiazepine diazepam (an anxiolytic) can cause an upregulation of hippocampal FGF2 mRNA.[70]

Effects of FGF Administration in Animals and Humans

Considering the functions of FGFs in neuroprotection and repair, one could ask whether patients with neuropsychiatric diseases might benefit from taking FGFs. Several preclinical studies have investigated the use of FGF2 in healthy as well as in injured rats, and 2 clinical trials in humans have been published. Early embryonic injection of FGF2 (at embryonic day 15.5) resulted in an increased volume (18%) and total number (87%) of neurons in the adult cerebral cortex, while later embryonic injection (at embryonic day 20.5) increased the number of glia.[71] In healthy adult animals, a denser dentate gyrus and hippocampus with more neurons was found after injecting FGF2 in the cerebrospinal fluid.[11,72] Beneficial effects of FGF have been reported in animal models of several neuropsychiatric conditions. When given to adult rats, FGF2 seems to have antidepressant-like properties.[11] After seizure, FGF2 can prevent cell loss in the hippocampus region, and it also has neurite-promoting effects.[39] FGF2, FGF13, and FGF18 reduce infarct volume and behavioral deficits after transient or permanent medial cerebral artery occlusion.[73,74] In addition, FGF8 is neuroprotective after oxidative stress of cultured hippocampal neurons.[75] The number of axonal branches was increased after FGF2 administration to a sciatic nerve lesion.[76] In monkeys treated with MPTP, which are a model for Parkinson's disease, intracerebral FGF2 infusion improved motor behavior and dopamine metabolism.[77] Lastly, significantly more rat fetal hippocampal CA3 neurons survived when they were transplanted into young adult hippocampus in the presence of FGF2 than without it.[78]

Human studies on using FGF fared less well: in 2 clinical trials with acute stroke patients, use of FGF2 led to higher mortality rates in the treatment group than in the control group due to hypotension, without significantly evident neuroprotection.[79] The problem in clinical use seems to lie in obtaining doses high enough to penetrate the blood-brain barrier, while minimizing peripheral side effects.

Summary of Findings

Reviewing the available studies, we found several lines of evidence, including functional plausibility, positional and functional genetic studies, knockout mouse models, effects of using FGF in animals and man, and associations between FGFs and environmental risk factors for schizophrenia, that all support a role for fibroblast growth factors in schizophrenia. We have summarized our findings in table 1.

Discussion

These findings show that the FGF system is involved in multiple processes that are likely involved in schizophrenia and that manipulation of FGFs and their receptors leads to schizophrenia-related phenotypes in rodents. Aberrations in the FGF system may constitute a more general risk factor for psychiatric illness because there are also observations supporting an involvement of FGFs in mood disorders.[11] Since there is considerable phenotypic overlap between the major psychiatric diagnoses,[21] this might well reflect an overlap in the pathophysiological mechanisms involved.

How can we integrate all these findings? From all this evidence, we could hypothesize that genetic variations in growth factors (*FGFs* and other factors like *BDNF*)

Table 1. Summary of Main Findings on FGFs and Schizophrenia

Research Area	Findings	Reference
Function of FGFs	• FGFs control growth and patterning, regulate neurogenesis, neuroprotection, and repair of neuronal tissues.	Reuss and von Bohlen und Halbach[8]
FGF and dopamine	• FGF2 leads to proliferation of dopamine precursor cells, while dopamine enhances FGF2 release.	Reuss and von Bohlen und Halbach,[8] Grothe and Timmer[15]
	• FGFs acts as a cotransmitter through the adenosine A_{2A} receptor to regulate synaptic plasticity and modulate the actions of dopamine.	Flajolet et al[26]
Human genetic studies	• A disrupted *NPAS3* gene cosegregates with illness in family with schizophrenia and a *NPAS3* deletion was shown to decrease *FGFR1 mRNA* expression by 80%.	Kamnasaran et al,[27] Pieper et al[28]
	• SNPs near *FGFR2* in *FGF1* and *FGFR1* are associated to schizophrenia, while a *FGF2 SNP* is associated to hippocampal volume in schizophrenia patients.	Jungerius et al,[30] Bakker et al,[31] O'Donovan et al[29]
	• *FGF1* and *FGF20* are located in replicated linkage regions for schizophrenia.	Badner and Gershon,[32] Lewis et al[33]
Animal genetic studies	• *FGFR1* knockout mice display "schizophrenia-like characteristics."	Klejbor et al,[24] Shin et al[36]
	• *FGF2* knockout mice show a decreased neuron number in the cerebral cortex.	Turner et al[11]
mRNA and protein expression	• FGFR2 mRNA in hippocampus of postmortem brains of schizophrenia patients is decreased.	Gaughran et al[42]
	• FGF2 protein levels in medicated schizophrenia patients are increased.	Hashimoto et al[41]
Environmental risk factors	• Cannabinoid receptor CB1 agonists mimic FGF2 response in axonal growth.	Williams et al[47]
	• Perinatal hypoxia and prenatal stress change FGF2 expression and FGF2 responsiveness in later life.	Riva et al,[20] Fumagalli et al[55]
	• FGF2 and FGFR1 mRNA in hippocampus is downregulated after social defeat.	Turner et al[58]
Medication	• FGF2 mRNA in hippocampus of postmortem brains of schizophrenia patients receiving clozapine is decreased.	Gaughran et al[42]
	• Long-term use of antidepressant drugs, quetinapine, clozapine, combined olanzapine and fluoxetine, and quinpirol upregulates FGF2 mRNA in rats.	Riva et al,[20] Riva et al,[62] Fumagalli et al,[63] Maragnoli et al,[65] Fumagalli et al[67]
FGF administration	• FGF2 administration leads to increased volume and number of neurons in adult cerebral cortex, hippocampus, and dentate gyrus.	Vaccarino et al,[71] Rai et al[72]
	• Beneficial effect from using FGF2 in rat models of depression, seizures, infarction, and Parkinson disease.	Turner et al,[11] Dono,[39] Ellsworth et al,[73] Yao et al,[74] Market al,[75] Fontan et al[77]

Note: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; NPAS3, neuronal PAS domain protein 3; mRNA, messenger RNA; SNP, single-nucleotide polymorphism.

increase the risk for developing psychiatric disorders in several ways. Because these growth factors play a role in neurodevelopment, they could lead to the subtle changes in brain structure encountered in schizophrenia. We know disturbed FGF signaling can influence dopamine signaling and neuronal proliferation and differentiation in the cerebral cortex. Dopamine disturbances and (prefrontal) cortical dysfunctions are both involved in schizophrenia and might exacerbate each other.[22]

Moreover, genetic variations in growth factors could lead to reduced plasticity and a compromised neuroprotection in response to environmental insults, both prenatally as well as later in life. The hippocampus is one of the brain regions where adult neurogenesis occurs,[80] and this allows the hippocampal network to adapt to the levels of novelty and complexity that an individual encounters lifelong. Not only stress and environmental factors influence hippocampal neurogenesis but also genetic factors, including *FGFR1, DISC1, reelin* and *neuregulin 1*.[80] Disturbed adult neurogenesis may result in prolonged developmental problems and some of the symptoms of schizophrenia. Growth factor expression during development is highly regulated, and the effect of environmental influences might therefore largely depend on the developmental phase in which they occur.

The data available suggest that fibroblast growth factors play a role in schizophrenia and related psychiatric disorders, but further research is necessary to indicate how the direction of the changes in FGF levels influence schizophrenia. During development, both increased and decreased FGF levels could cause aberrations in the brain, while in later life a decreased neuroprotection may be seen after decreased FGF. It is likely that the effects of FGFs are, at least in part, mediated through genetic variations in *FGF* genes, which makes them excellent candidate genes for schizophrenia and other major psychiatric disorders.

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